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The Honorable Henry A. Waxman
Ranking Minority Member
Committee on Government Reform
and Oversight
House of Representatives
Washington, D.C. 20515

Dear Mr. Waxman:

This is in response to your letter of July 23, 1998, co-signed by Ranking Minority Members John D. Dingell and Sherrod Brown, concerning the Food and Drug Administration's (FDA) proposed rule implementing section 401 of the Food and Drug Administration Modernization Act of 1997. We thank you for your comments to Docket No. 98N-0222 on the Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices.

Your interest and comments are appreciated. Please be assured that your comments will be considered in preparation of the final rule. A similar letter is being sent to your co-signers.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

bcc: HFW-10
HFW-2
HFW-14
HFA-305
R/D: LPalmer 7/30/98
Review: J. Dupont 8/2/98
Review: B.Shultz 8/26/98
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Congress of the United States

House of Representatives

Washington, DC 20515

July 23, 1998

Dr. Michael A. Friedman
Acting Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Rm. 1-23
Rockville, MD 20857

Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices; Docket No. 98N-0222

Dear Dr. Friedman,

We are writing to support and comment upon the Food and Drug Administration's (FDA) proposed rule implementing section 401 of the Food and Drug Administration Modernization Act of 1997 (FDAMA, Pub. Law 105-115). We believe that the proposed rule properly reflects the Congress' statutory intent in enacting this provision, and achieves the important goals of assuring the public health and encouraging the dissemination of important health information.

Statutory Intent of Section 401

We wish to strongly emphasize that the principal policy considerations underlying enactment of section 401 were twofold: first and foremost, to ensure that the financial and legal incentives for manufacturers to seek approval of supplemental uses of prescription drugs and medical devices remain intact; and second, to give medical providers and their patients a method of obtaining scientific information regarding unapproved drug or device uses which did not undermine these incentives or the existing statutory assurances of safety and efficacy.

The key to understanding section 401 is to recognize that health providers and patients alike are exposed to myriad sources of information regarding unapproved drug and device uses. Peer review journals, continuing medical education, medical publishers, professional medical societies, patient associations, Internet-based government and commercial information services, and mass media all offer a wealth of information about the latest clinical trials, the latest research findings and the prevailing standards of medical care. At the same time, however, patients consistently face difficulties obtaining reimbursement from health insurers for unapproved drug and device uses on the grounds that they are unapproved by the FDA.

Recognizing that the health care market was not suffering from a lack of reliable and timely information regarding such uses, but that patients would benefit from the timely approval of such uses, Congress' fundamental challenge prior to enactment of FDAMA was how to promote the submission of supplemental use applications. The interest of regulated industries in obtaining statutory revisions which would permit the advertising and promotion of unapproved drug and device uses afforded Congress an opportunity to achieve the goal of encouraging the

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submission of supplemental use applications while simultaneously creating a discrete, experimental program for the dissemination of information about unapproved drug and device uses by regulated industries.

As the conference report on S. 830 states:

> The conference agreement's inclusion of this section is intended to provide that health care practitioners can obtain important scientific information about uses that are not included in the approved labeling of drugs, biological products, and devices. The conferees also wish to encourage that these new uses be included on the product label. Therefore, the agreement includes strong incentives to conduct the research needed and file a supplemental application for such uses.

We believe that the FDA's proposed rule reflects a proper balance in achieving Congress' intended goals of encouraging the approval of unapproved drug and device uses, while creating a time-limited opportunity to determine whether the dissemination of information regarding such uses by regulated industries, motivated by strong commercial and promotional interests, serves the public health.

Disseminated information must be complete and balanced

We also agree that the proposed rule appropriately addresses the need for complete and balanced presentation of information by supplement sponsors. Proposed section 99.101 appropriately calls for the presentation of a clinical investigation to be "reasonably comprehensive." Article abstracts would fail to meet the high statutory standard for complete, balanced information. This is also consistent with the congressional intent that recipients have complete information at their disposal. Similarly, this section is entirely in accord with the intent underlying specific statutory requirements that journal articles be unabridged and reference publications unexcepted; that a bibliography of other articles regarding the unapproved use be provided; and that additional information may be required to be distributed if the original dissemination was not "objective and balanced."

Exceptions to filing supplements must be narrow

Perhaps the most important section of the proposed rule relates to the statutory exceptions from the filing of a supplemental use application. It was Congress' intent that any dissemination be predicated on submission of such an application. Any exceptions to this rule were intended to be limited in scope and rare in frequency.

The factors outlined in proposed sections 99.205 and 99.305 are wholly consistent with the statute. The law requires that the Secretary consider the patent or marketing exclusivity available to a sponsor, the size of the patient population expected to benefit from a supplemental approval, and whether it would be unethical to conduct the studies necessary for such an approval.

In cases where a supplemental use application would be economically prohibitive, section 401 was intended to create narrow circumstances under which the dissemination of information could take place in the absence of an application. Anything else would do violence to the balancing of interests and goals achieved by this provision. As Abbey Meyers, president of the National Organization for Rare Disorders, wrote to us on September 25, 1997, "If a patient population is considered a large enough 'market' to justify a company engaging in active promotion of an off-label use of a product, there is no doubt that a real potential for profit exists."

The proposed rule fully reflects this critical statutory balance and the requirements stipulated by the agency to be met by sponsors in obtaining an exemption from filing would provide information essential to determining whether such exemptions are appropriate, justified and consistent with the statute.

Public access to clinical trial information and public participation in granting of exemptions

Consistent with the intention of Congress to expand the public's access to information regarding clinical trials, as manifest in FDAMA sections 113 and 130, we believe that the agency should provide for public access to information made available under section 401 and seek public input regarding the granting of exemptions from the filing of supplemental applications. The public and patient communities are the essential stakeholders in the determinations made under section 401 and should be afforded the opportunity to share their inherent expertise with the agency.

Public participation in the exemption process and public access to information regarding trials initiated in support of supplemental filings is consistent with the intentions of Congress in enacting FDAMA. The inappropriate granting of exemptions, for example, would be contrary to Congress' intent, as stated in the Act's findings: the "prompt approval of safe and effective new drugs and other therapies is critical to the improvement of the public health so that patients may enjoy the benefits provided by these therapies to treat and prevent illness and disease."

Section 401 is a pilot program

While "off-label" uses have traditionally been viewed by the FDA as being within the practice of medicine and subject to the judgement of health professionals, section 401 was intended by Congress only to create a pilot program of limited duration which linked the submission of supplemental use applications to the dissemination of information by regulated industries. We believe the proposed rule reflects congressional intent, applaud the agency's work to date in implementing FDAMA in a timely manner and look forward to working with the agency to determine whether section 401 truly serves the public health.

Sincerely,

JOHN D. DINGELL
Ranking Member
House Committee on Commerce

SHERROD BROWN
Ranking Member
House Commerce Subcommittee on
Health and the Environment

HENRY A. WAXMAN
Ranking Member
House Committee on Government
Reform and Oversight

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Public Participation

FDA should provide for public access to information made available under section 401 to the maximum extent feasible. The patients' groups are essential stakeholders in the exemptions granted under section 401 and their participation is crucial to successful implementation of this provision.

Journal articles

Congress intended for FDA to have a role in assessing the scientific acceptability of journal articles and reference texts distributed pursuant to section 401. The statute requires that the information be a "copy of an article, peer-reviewed by experts qualified by scientific training or experience . . . which is about a clinical investigation . . . and which would be considered to be scientifically sound by such experts." Where appropriate, the FDA may require the manufacturer to disseminate additional objective and scientifically sound information that pertains to the safety or effectiveness of the use and is necessary to provide objectivity and balance, or the Secretary may provide her own objective statement. Thus, the statute clearly envisions that the Secretary be provided sufficient information to assess the clinical investigation. This opportunity is especially important in order for the Secretary to meaningfully assess the need for balancing information and to assess whether the information is false or misleading.

Exemptions to filing supplements

Congressional intent is clear. Congress intended that dissemination be predicated on submission of a supplemental use application. Exceptions to this rule are limited in scope and should be infrequent. Any interpretation to the contrary would undermine the essential compromise reached in this legislation. As stated in the conference report, "there *may be limited circumstances* when it is appropriate to exempt a manufacturer from the requirement to file a supplemental application." (emphasis added.)

The authority that Congress gave to the Secretary regarding factors to be taken into account in granting exemptions is permissive, not mandatory. Congress intended the Secretary to exercise substantial discretion in granting exceptions and that only when the interests of public health are served by allowing the exemption and there is no significant possibility that a supplemental application will be filed should FDA grant such an exemption.

Sincerely,

Edward M. Kennedy